August 26, 2022

Dear CEO or President:

This letter concerns unapproved prescription drug products containing salsalate, a nonsteroidal anti-inflammatory drug (NSAID) manufactured, repackaged, relabeled, or distributed by your firm. Your firm is receiving this letter based on drug registration and listing information provided to the Food and Drug Administration (FDA). As described below, your firm should take prompt action to relabel your prescription drug product(s) containing salsalate to reflect clinical evidence that the use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

Background

Your salsalate is an unapproved NSAID product labeled for the relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis and related rheumatic disorders. FDA determined that NSAID products, including salsalate, represent a class of products that have the potential for the serious risks of fetal renal dysfunction, oligohydramnios, and neonatal renal impairment.

FDA uses a risk-based approach for prioritizing our regulatory and enforcement actions involving unapproved new drugs. As such, FDA intends to exercise regulatory discretion for the marketing of unapproved salsalate, barring new safety or regulatory concerns, as long as the labeling of unapproved salsalate products contains the requested labeling revisions specified in this letter to address and mitigate the risk of oligohydramnios and neonatal renal impairment in pregnant women using salsalate.

Fetal Renal Dysfunction/ Oligohydramnios/ Neonatal Renal Impairment Associated with NSAIDs

FDA is aware of case reports submitted to FDA's Adverse Event Reporting System and published in the medical literature describing that use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. We have determined that NSAID products represent a class of products that have the potential for the serious risks of fetal renal dysfunction, oligohydramnios, and neonatal renal impairment.

Requested Labeling Revision

In October 2020, FDA published a Drug Safety Communication notifying consumers, health care providers, and manufacturers of the risks of oligohydramnios and serious renal impairment in

neonates associated with NSAIDs use at 20 weeks gestation or later in pregnancy.[1] In this communication, FDA recommended avoiding NSAIDS in pregnant women at 20 weeks or later in pregnancy rather than the 30 weeks previously described in NSAID prescribing information. If deemed necessary by a health care professional, use of NSAIDs between 20 and 30 weeks of pregnancy should be limited to the lowest effective dose for the shortest duration.

FDA further required manufacturers of FDA-approved prescription NSAIDs to standardize warning information about the risk of oligohydramnios and neonatal renal impairment in product labeling across this class of products.[2]

Based on the safety concerns described above and to ensure consistency with the information in the FDA-approved NSAID prescribing information, FDA believes that the labeling for unapproved prescription drug products containing salsalate should include the following language, which is included in safety labeling change notification letter for FDA-approved NSAIDs and can also be found on FDA's website at https://www.fda.gov/media/144260/download.

Instructions for each section are indicated in *(italics)*

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

Replace Premature Closure of the Ductus Arteriosus *with the following:*

• Fetal Toxicity: Limit use of NSAIDs, including TRADENAME, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.X, 8.1).

----------USE IN SPECIFIC POPULATIONS----------

Delete the bullet, Pregnancy*, under* USE IN SPECIFIC POPULATIONS.

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

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[1] See, e.g., "FDA Drug Safety Communication: FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid" (October 16, 2020), *available at* https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-avoiding-use-nsaids-pregnancy-20-weeks-or-later-because-they-can-result-low-amniotic

[2] Manufacturers of approved, prescription NSAIDs were given 30 days to reply to the Agency's letter regarding these new Safety Labeling Changes. See https://www.fda.gov/media/144260/download#:~:text=Avoid%20use%20of%20NSAIDs%2C%20including,at%20approximately%20this%20gestational%20age.

Change **5.X Premature Closure of the Ductus Arteriosus** *to* **5.X Fetal Toxicity** *and replace existing text with the text shown below.*

5.X Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including TRADENAME, in pregnant women at about 30 weeks gestation and later. NSAIDs, including TRADENAME, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including TRADENAME, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit TRADENAME use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if TRADENAME treatment extends beyond 48 hours. Discontinue TRADENAME if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

Update the **8.1 Pregnancy** *subsection as shown below.*

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including TRADENAME, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of TRADENAME use between about 20 and 30 weeks of gestation, and avoid TRADENAME use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including TRADENAME, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies … ***(Note to Applicant:*** *Existing risk summary statement(s) based on animal data should be included here.)* Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as [active moiety], resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Above the subheader titled, **Labor and Delivery***, add the following:*

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including TRADENAME, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If TRADENAME treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue TRADENAME and follow up according to clinical practice (*see Data*).

Data

Human Data

***Note to Applicant**: Insert the following language after any existing information regarding human data:*

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

***Note to Applicant:** Include description of animal studies here as appropriate.*

17 PATIENT COUNSELING INFORMATION

Insert new language at the end of the subsection titled, Fetal Toxicity*, and move cross references to the end.*

Fetal Toxicity

Inform pregnant women to avoid use of TRADENAME and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with TRADENAME is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to

be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.X) and Use in Specific Populations (8.1)*].

MEDICATION GUIDE

In the section, **Before taking NSAIDS,…**, *update the bullet "*are pregnant or plan to become pregnant*…" as shown below. Deletions indicated by strikethrough, additions by underline.*

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:

• are pregnant or plan to become pregnant. ~~Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy.~~ Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after ~~29~~ about 30 weeks of pregnancy.**

Conclusion

Based on the currently available information about the risk of oligohydramnios and neonatal renal impairment in pregnant women using NSAIDs at about 20 weeks of pregnancy, and consistent with the FDA's risk-based approach to marketed unapproved drugs, FDA intends to exercise enforcement discretion for the marketing of unapproved salsalate, barring new safety or regulatory concerns, as long as the labeling of unapproved salsalate products contains the requested labeling revisions specified in this letter to address and mitigate the risk of oligohydramnios and neonatal renal impairment in pregnant women using salsalate.

Please note that all firms are required to electronically update the listing, including labeling, of their products under section 510(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) if there is any material change in any of the information previously submitted in the listing. Specifically, registrants of establishments that manufacture, repack, relabel, or salvage prescription drugs must review and update their drug listing information each June and December.[3] Registrants that discontinue the marketing of their products must submit a delisting for each product's National Drug Code. Registrants must submit any material changes in the labeling of their products and any other information previously submitted pursuant to 21 C.F.R § 207.49 or other relevant sections of part 207.[4] Registrants are encouraged to update listing information at the time of any change affecting information previously submitted.[5]

FDA continues to review information regarding the risks of fetal renal dysfunction, oligohydramnios, and neonatal renal impairment posed by drug products containing salsalate and may consider additional regulatory action in the future to address this serious health risk.

[3] 21 C.F.R. § 207.57(b).
[4] Id.
[5] Id. at § 207.57(c).

Furthermore, FDA intends to continue to enforce the new drug approval requirements of the FD&C Act to achieve the public health objectives of the statute and FDA will continue to evaluate its risk-based prioritization for salsalate in light of all the facts of a given circumstance. We encourage manufactures and distributors of marketed unapproved new drugs to obtain approval for these drugs. Please contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710 for assistance in communicating with the FDA on the application process for your unapproved salsalate product.

If you have any questions about the contents of this letter, please contact FDAADVISORY@fda.hhs.gov.

Sincerely,

Carolyn Becker
Director
Office of Unapproved Drugs and Labeling Compliance
Office of Compliance
Center for Drug Evaluation and Research